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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : CAROLINE S. BROWN

Serial No. : 07/838,715 Examiner M. Tuscan
Art Unit 1813

Filed : May 4, 1992

For : HUMAN PARVOVIRUS B19 PROTEINS AND VIRUS-LIKE PARTICLES, THEIR PRODUCTION, AND THEIR USE IN DIAGNOSTIC ASSAYS AND VACCINES

June 17, 1993

Honorable Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

A M E N D M E N T

This amendment is in response to the Office Action dated December 17, 1992. A Preliminary Amendment dated March 13, 1992 has already been filed.

In the Office Action the Examiner has required applicant to affirm applicant's election of Invention I, Claims 1, 12-15, 26-28, 37-39 and 47-48. Applicant hereby affirms the election of Invention I claims for prosecution in this application. The election of Invention I claims was made with traverse. It is respectfully requested, therefore, that the Examiner reconsider,

modify and/or withdraw the indicated requirement for restriction.

It is respectfully submitted that all the claims pending in this application are directed essentially to the same invention as set forth in originally submitted Claim 1 directed to a recombinant, non-fused VP1 protein of the human parvovirus B19. This VP1 protein is made in accordance with this invention in Spodoptera frugiperda cells employing a baculovirus expression vector system containing genetic information for the expression of the parvovirus B19 protein VP1. In view of these comments it is respectfully requested that the Examiner reconsider and withdraw the indicated requirement for restriction and examine on the merits all the claims presented in this application, Claims 1-48.

In the Office Action the Examiner rejected Claims 12, 13, 26, 27, 37, 38, 47, 48 based on 35 U.S.C. 101 as lacking patentable utility. According to the Examiner, the specification fails to provide evidence of the patentable utility, noting that it is well established, according to the Examiner, that a patent may not be granted on a chemical compound unless utility is known.

The Examiner also noted that the specification is objectionable under 35 U.S.C. 112, first paragraph, as failing to adequately teach how to make or use the invention, i.e. as lacking an enabling disclosure. In this connection the Examiner noted that the use of the claimed recombinant protein and particles as a vaccine, as in

Claims 12-13, 26-27, 37=38 and 47-48, is not taught in the specification. The Examiner also mentioned that the specification fails to provide evidence of an effective adjuvant to be used with the vaccine as in Claims 12, 26, 37 and 47.

Additionally, with respect to the specification, the Examiner called attention to the term "antigenically active" and the Examiner noted that the specification fails to describe the construction of recombinant baculovirus vectors containing epitopes of proteins.

It is respectfully requested that the Examiner reconsider and withdraw the indicated objections to the specification as set forth hereinabove. The Examiner is referred to the complete specification and particularly Fig. 1 which shows in outline the formation of a baculovirus expression vector system for the recombinant production of non-fused VP1 protein of the human parvovirus B19, all in accordance with this invention. It is in the light of the complete disclosure of the specification and Fig. 1 that the Examiner is requested to reconsider and withdraw the indicated objection to the specification.

The Examiner, in addition to objecting to the specification, also objected to the claims. For example, in addition to objecting to Claims 12-13, 26-28, 37-39, 47-48, the Examiner noted that certain of these claims are indefinite and other of these claims

are vague, particularly with respect to the recitation "antigenically active portion" and "carrier." The Examiner also objected to certain of the claims, Claims 13, 27 and 28 as being in improper independent form. With respect to these claims it is requested that the Examiner reconsider and withdraw this objection to the claims. It is submitted that a careful reading of the claims will bring to light that these claims are in proper form for examination.

With respect to the prior art, the Examiner stated that Claims 1 and 14 are anticipated by the Ozawa et al publication, Journal of Virology Reference S. Additionally, Claims 1, 12 and 13 were rejected as obvious in view of the disclosures of another Ozawa et al publication, Journal of Virology Reference T, along with the Sisk et al and Cotmore et al publication references in view of Smith et al, Pennock et al, Luckow et al publication references and Wood et al U.S. 4,971,793. According to the Examiner, these references in combination, as recited on pages 9-12 of the Office Action, make obvious to one skilled in the art, absent unexpected results to clone the coating sequence for VP1 into a baculovirus expression vector.

Claims 14-26 and 27 were also rejected by the Examiner as obvious in view of the Ozawa et al Journal of Virology publication, Reference T, together with Cotmore et al, Sisk et al, in view of Smith et al, Pennock et al, Luckow et al and the Wood et al

references. According to the Examiner, as recited on pages 13 and 14 of the Office Action, it would have been obvious to clone the coding sequence for VP2 into a baculovirus expression vector to produce large quantities of capsid antigen for use in a vaccine composition.

Claims 15, 28, 37 and 38 were rejected by the Examiner as obvious over Ozawa et al et al Journal of Virology, Reference T, together with Cotmore et al, Sisk et al, Smith et al, Pennock et al, Luckow et al and Wood et al in view of other publication references, Kajigaya et al, Pintel et al and Mazzara et al, for the reasons indicated on pages 14 and 15 of the Office Action, viz. it would have been obvious based on the disclosures of this extended combination of references to produce empty virions consisting of VP2 or VP1 and VP2 in the baculovirus expression system and for their use in vaccine compositions.

Finally, Claims 39 and 47-48 were rejected based on the combination of the above-cited references including additionally the publication references and Evans et al, Borisova et al and Clarke et al. According to the Examiner it would be obvious to one skilled in the art, absent unexpected results, in the light of these references, to insert the antigenic epitopes of other pathogens in the parvovirus VP2 coding sequence, to express the chimeric gene in the baculovirus-insect cell expression system and produce empty capsid particles expressing the foreign antigenic

epitopes on the particle surface.

Applicant has carefully considered the disclosures of the references cited by the Examiner and the Examiner's indicated basis for the rejection of claims on these references. It is applicant's position that the claimed invention would not be obvious from the teachings and disclosures of these references, separately or in any proper combination, absent applicant's disclosure. It is further submitted that the Examiner could only have made the indicated combination of the disclosures of the references cited as basis for the rejection of applicant's claims by way of hindsight and in the light of applicant's own teachings and disclosure. It is respectfully requested, therefore, that the Examiner reconsider and withdraw the indicated rejections of the claims on the combinations of the references cited.

Additionally, applicant make the following comments. With respect to the rejection of the claims as lacking utility, applicant calls to the Examiner's attention that there are publications showing antibodies raised against the B19 capsid proteins provide protection against B19 infections, viz. G.J. Kurtzman et al publication J. Clin. Invest. 84, 1114-1123 (1988). A copy of this publication has not yet been received by applicant's attorney but, when received, will be forwarded to the Examiner. Further, applicant mentions that there are data showing that B19 virus and VP2/VP1 particles for antigenic determinants in common

and that naturally antibodies bind to the recombinant particles, see Brown et al J. Virol. 66, 6989-6996 (1992). A copy of this publication will also be provided the Examiner by applicant. Applicant also points out that animal tests with recombinant VP2 particles having an insertion of epitopes or other pathogens have been carried out and these tests have revealed that such particles (VP2 with a foreign epitope inserted therein) are immunogenic against a challenge infection. A publication directed to the results of these tests is in preparation and will be forwarded to the Examiner. More pertinent, it is pointed out to the Examiner that the method of administration, amounts, immunization schedule and adjuvant and challenge dosages are set forth in this to-be-published manuscript.

Concerning the rejection of the claims based on 35 U.S.C. 112 as lacking an enabling disclosure, it is applicant's position that the specification provides adequate and complete information to enable one skilled in the art to practice applicant's invention. Mere covnentional details known to those skilled in the art have not always been set forth as being unnecessary to teach one skilled in the art applicant's invention. Concerning applicant's use of the term "antigenically active portion" in the claims, it should be observed that a vaccine may be based on a number of the disclosed proteins, whole or peptides thereof, which represent an immunogenic epitope of these proteins, such as the VP between amino acids 259-426 which comprises an important antigenic domain.

With respect to the Examiner' objection to the use of the word "carrier", it is pointed out that in vaccine compositions the word "carrier" conventionally references to substances like solvents and diluents that are utilized with the active components of the vaccine in the formation of the vaccine preparation. Accordingly, the Examiner is requested to reconsider and withdraw any indicated objection to the use of the term "carrier" in the claims as well as to the use of the term "antigenically active" in the claims.

With respect to the rejection of the claims based on 35 U.S.C. 112, fourth paragraph, it is mentioned that Claims 13, 27 and 48 are different claims and are directed to a use or process whereas Claims 12, 26 and 47 are composition claims. If necessary, applicants would be pleased to rewrite Claims 18, 27 and 28 to further distinguish these claims from the other claims in this application.

With respect to the references cited by the Examiner, the following comments are made. Concerning the Kajigaya et al and Borisova references, the priority date of these references is subsequent to the priority date of this application and, therefore, it is submitted, are not appropriate prior art references.

Further, applicant wish to call attention to and emphasize the following aspects and achievements of applicant's invention.

One of the surprising achievements of the invention is the production of VP2 particles by recombinant insect cells which express VP2 but not VP1.

Native parvovirus B19 has a capsid consisting of the two capsid proteins, VP1 and VP2. The capsid has an isometric symmetry for which protein-protein interactions play an important role in contrast to capsids having a helicoidal capsid symmetry for which protein-nucleic acid interactions are decisive for the structure of the capsid particle.

Isometrical capsids can be composed of identical copies of a single protein or of two or more different proteins. In the case that the capsid is composed of many different proteins, it may be likely and expected that the elimination of one of said proteins will not be detrimmental to formation of capsid particles. In the case of human parvovirus B19, however, the capsid is composed of only two different proteins, VP1 and VP2. In such a case, a person skilled in the art would rather expect that the absence of one of these proteins would prevent the formation of capsid particles. In this respect, please note that the function of the proteins VP1 and VP2 in the parvovirus B19 capsid formation and stability was unknown at the priority date. In addition, there had not been any description of a formation of VP2 particles before the priority date.

It was not a surprising finding that the expression of VP1 in the absence of co-expression of VP2 failed to produce any particles. Totally unexpected, however, the expression of VP2 did produce particles, even in the absence of VP1 expression.

The production of capsid particles which are composed exclusively of protein VP2 entails particular advantages. A first advantage is that co-transfection or co-infection of insect cells with two different recombinant baculoviruses to obtain transient co-expression of VP1 and VP2 can be circumvented. A second advantage is that particles exclusively composed of VP2 are much more homogeneous than particles formed from co-expressed VP1 and VP2. In this respect, it is observed that the expression of VP1 and VP2 are parvovirus B19-infected cells is strictly regulated, VP2 being formed in a particular excess in relation to VP1. Up till know, it has not been possible to mimic the regulation of expression and the correct ratio of VP2 and VP1 in recombinant expression systems.

Highly surprising is also the high antigenicity of VP2 particles. It is impossible to predict beforehand which antigen of a particular virus can be used as a diagnostic marker. As far as human parvovirus B19 is concerned, it was unknown at the priority date that VP2 particles could exist and would be useful, e.g. in and ELISA, to detect parvovirus-specific antibodies of the IgM and IgG type, as has been demonstrated by experiments using sera from

individuals having a proven parvovirus infection. This could not have been predicted. Until this invention, screening and diagnosis had been based on the use of native virus particles containing both VP1 and VP2.

Another surprising achievement of the invention is the use of empty parvovirus B19 VP2 capsids as carrier of heterologous epitopes.

It is essential for utility of chimaeric particles as a vaccine that they are capable of inducing an immunologic memory for the heterologous epitopes. The most important components of such memory are T-helper lymphocytes. The fact is that carrier particles which themselves contain an immunodominant T-helper epitope, frustrate the stimulation of T-helper lymphocytes against a heterologous T-helper epitope carried by said carrier particles.

It has recently been demonstrated that T-cell epitopes of Hepatitis B core antigen do interfere with heterologous T-cell epitopes (Schodel et al., J. Virol. 66, 106-114, 1992). This is a significant disadvantage of the use of Hepatitis B core antigen as a carrier for heterologus epitopes.

In contrast therewith, neither native parvovirus B19 nor empty recombinant VP2 capsids according to the invention stimulate T-lymphocytes of parvovirus-infected individuals (see Kurtzman et al

referred to hereinabove). In view thereof, it is considered to be plausible that in the case of chimaeric parvovirus B19 VP2 capsids according to the invention there will not be interference of parvovirus epitopes with heterologous T-cell epitopes carried by said particles.

Therefore, in view of the foregoing remrks, reconsideration of the rejection of the claims, particularly on the references cited, together with reconsideration of the requirement for restrtiction, favorable consideration of the elected invention claims and allowance of all the pending claims are earnestly solicited.

I hereby certify that this paper is being deposited this date with the U.S. Postal Service in first class mail addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231

Thomas F. Moran June 17, 1993
Thomas F. Moran Date
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Respectfully submitted,

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